PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61B 5/055, A61K 51/00	A1	(11) International Publication Number: WO 97/01304
		(43) International Publication Date: 16 January 1997 (16.01.97)

(21) International Application Number: PCT/US96/10808

(22) International Filing Date: 25 June 1996 (25.06.96)

(30) Priority Data:
08/496,645 29 June 1995 (29.06.95) US

(71) Applicant: MALLINCKRODT MEDICAL, INC. [US/US]; 675 McDonnell Boulevard, P.O. Box 5840, St. Louis, MO 63134 (US).

(72) Inventors: BRODACK, James, W.; 3827 Kentucky Derby Drive, Florissant, MO 63034 (US). DEUTSCH, Edward, A.; 12805 Maryland Estates Court, Maryland Heights, MO 63043 (US). DEUTSCH, Karen, E.; 12805 Maryland Estates Court, Maryland Heights, MO 63043 (US).

(74) Agents: MCBRIDE, Thomas, P. et al.; Mallinckrodt Medical, Inc., 675 McDonnell Boulevard, P.O. Box 5840, St. Louis, MO 63134 (US).

(81) Designated States: CA, JP, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: RADIOLABELED APATITE PARTICLES CONTAINING A PARAMAGNETIC ION

(57) Abstract

The present invention provides methods and compositions for improved medical diagnostic imaging and therapy for the treatment of rheumatoid arthritis. The compositions are derived from apatite particles including, but not limited to, hydroxyapatite, fluoroapatite, iodoapatite, carbonate-apatite, and mixtures and derivatives thereof. The compositions of the present invention contain a paramagnetic species incorporated into the apatite particles to improve magnetic resonance contrast and a radionuclide capable of providing a therapeutic dose of radioactivity. Also disclosed is a combination diagnostic/therapeutic composition and methods of performing medical diagnostic and therapeutic procedures which involve administering to a warm-blooded animal an amount of the above-described apatite particles containing a diagnostically effective amount of the paramagnetic ion and a therapeutically effective amount of the radionuclide and then performing the medical treatment and diagnostic procedures.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	**GB**	United Kingdom	**MW**	Malawi
AT	Austria	**GE**	Georgia	**MX**	Mexico
AU	Australia	**GN**	Guinea	**NE**	Niger
BB	Barbados	**GR**	Greece	**NL**	Netherlands
BE	Belgium	**HU**	Hungary	**NO**	Norway
BF	Burkina Faso	**IE**	Ireland	**NZ**	New Zealand
BG	Bulgaria	**IT**	Italy	**PL**	Poland
BJ	Benin	**JP**	Japan	**PT**	Portugal
BR	Brazil	**KE**	Kenya	**RO**	Romania
BY	Belarus	**KG**	Kyrgystan	**RU**	Russian Federation
CA	Canada	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CF	Central African Republic			**SE**	Sweden
CG	Congo	**KR**	Republic of Korea	**SG**	Singapore
CH	Switzerland	**KZ**	Kazakhstan	**SI**	Slovenia
CI	Côte d'Ivoire	**LI**	Liechtenstein	**SK**	Slovakia
CM	Cameroon	**LK**	Sri Lanka	**SN**	Senegal
CN	China	**LR**	Liberia	**SZ**	Swaziland
CS	Czechoslovakia	**LT**	Lithuania	**TD**	Chad
CZ	Czech Republic	**LU**	Luxembourg	**TG**	Togo
DE	Germany	**LV**	Latvia	**TJ**	Tajikistan
DK	Denmark	**MC**	Monaco	**TT**	Trinidad and Tobago
EE	Estonia	**MD**	Republic of Moldova	**UA**	Ukraine
ES	Spain	**MG**	Madagascar	**UG**	Uganda
FI	Finland	**ML**	Mali	**US**	United States of America
FR	France	**MN**	Mongolia	**UZ**	Uzbekistan
GA	Gabon	**MR**	Mauritania	**VN**	Viet Nam

RADIOLABELED APATITE PARTICLES CONTAINING A PARAMAGNETIC ION

Field of the Invention

This invention relates in general to a radiolabeled paramagnetic compound for the simultaneous therapy and imaging of an individual afflicted with inflammatory arthropathy.

Background of the Invention

Over two million people in the United States suffer from rheumatoid arthritis. The major cause of pain and physical disability for these individuals comes from destruction of the diarthroidal or synovial joints. The disease will involve the hands (metacarpophalangeal joints), elbows, wrists, ankles and shoulders for most of these patients, and over half will have affected knee joints. Untreated, the joint linings become increasingly inflamed resulting in pain, loss of motion and destruction of articular cartilage. One medical therapy applied to this disease involves the use of chemicals to attack and destroy the inflamed synovium (chemical synovectomy); however, the agents employed are systemically and locally toxic and capable of damaging articular cartilage. Similar toxicity concerns arise when repeated injections of corticoid steroids are used. In several cases where chemical therapy has failed, surgery is employed to remove the inflamed joint lining (surgical synovectomy). The difficulty of removing all the diseased synovium, however, often leads to

regrowth with recurrence of symptoms. If surgery is successful, freedom from symptoms usually lasts two to five years. When the symptoms reappear, surgical reintervention is not an option due to the presence of fibrosis and scar tissue which result from the previous surgery.

Radiation synovectomy is an alternate treatment method that has been used for many years to substantially ablate or destroy the inflamed synovium. The procedure is simple, involving only the injection of a radionuclide of the appropriate characteristics into the synovial cavity. The primary disadvantage of this technique has been the unacceptable radiation doses to non-target organ systems due to leakage of radioactive material from the cavity and difficulty in delivering a β-particle of the appropriate energy for the size joint being treated. The chemical nature of current radiation synovectomy agents is such that leaked materials tend to be retained by liver, spleen and lymph nodes. The leakage problem is often due either to the difficulty of formulating the correct particle size or to lack of a tight binding of the nuclide to the particle. Another disadvantage is the use of radionuclides that do not have the appropriate beta energy to treat the inflamed synovium. In U.S. Patent No. 5,320,824, Brodack et al. describe a radiation synovectomy composition comprised of a radiolabeled insoluble compound, preferably hydroxyapatite, that solves these problems.

As an adjunct to treatment of inflammatory arthropathic diseases such as rheumatoid arthritis with a radiation synovectomy composition, it would be desirable to be able to better define the synovial tissue boundaries for improved diagnosis of the extent of the inflammation and to quantify improvement in the synovium of the afflicted joint . This is sometimes done by administering a separate MRI contrast agent intra-articularly into the afflicted joint to enhance the difference between the synovial fluid and surrounding bone and cartilage in the joint. Because the MRI agent and the

radiation synovectomy agent are typically chemically distinct and have different chemical and biological properties, e.g., distribution in the joint, one cannot be certain that the image obtained from the MRI agent accurately represents the effect of the synovectomy agent and that relevant or accurate data are being provided.

A need exists, therefore, for a compound and a method for the simulataneous treatment and imaging of a joint afflicted with inflammatory arthropathy that provides accurate and reliable results regarding the distribution of the synovectomy agent and its effect on the inflamed synovium.

Summary of the Invention

The present invention provides methods and compositions for improved medical diagnostic imaging and therapy for the treatment of diseases such as rheumatoid arthritis. The compositions are derived from apatite particles including, but not limited to, hydroxyapatite (sometimes referred to as "hydroxylapatite"), fluoroapatite, iodoapatite, carbonate-apatite, and mixtures and derivatives thereof. As used herein, the term fluoroapatite includes pure fluoroapatite as well as mixtures of fluoroapatite, hydroxyapatite, iodoapatite, and carbonate-apatite. Likewise, hydroxyapatite, iodoapatite, and carbonate-apatite are intended to include the pure and mixed forms. Since hydroxyapatite is a natural bone constituent, it is well tolerated and generally safe.

The compositions of the present invention contain a paramagnetic species incorporated into the apatite particles to improve magnetic resonance contrast and a radionuclide capable of providing a therapeutic dose of radioactivity. The apatite particles may also be fluorinated to form stable, fluoroapatite compositions useful for ^{19}F imaging. Incorporating a paramagnetic metal species in fluoroapatite or hydroxyapatite particles may

reduce ^{19}F and proton relaxivity, thereby enhancing MRI, MRS, or MRSI.

Also disclosed is a combination diagnostic/therapeutic composition and methods of performing medical diagnostic and therapeutic procedures which involve administering to a warm-blooded animal an amount of the above-described apatite particles containing a diagnostically effective amount of the paramagnetic ion and a therapeutically effective amount of the radionuclide and then performing the medical treatment and diagnostic procedures.

Among the many features and advantages of the present invention include the provision of a radiation synovectomy composition to treat inflamed synovia of people afflicted with rheumatoid arthritis and permit imaging of the afflicted joint by MRI; the provision of a composition that permits evaluation of proper distribution of the particles in the inflamed synovia by MRI; the provision of a composition that permits the effect of the radiation to be evaluated and monitored during its course of activity by MRI; and the provision of a composition that by the nature of the labelling process, any in vivo decomposition that generates joint leakage produces radioactive materials in a form that clear rapidly from the body.

Detailed Description of the Preferred Embodiments

The present invention provides methods and compositions for improved medical diagnostic imaging and therapy for inflammation arthropathy, including rheumatoid arthritis. As used herein, medical diagnostic imaging includes magnetic resonance imaging ("MRI"), magnetic resonance spectroscopy ("MRS"), magnetic resonance spectroscopy imaging ("MRSI") and therapy includes radiation synovectomy. The compositions of the present invention are derived from apatite or apatite-like particles.

The radiation synovectomy aspect of the composition is useful for treating, e.g., by ablation, the inflamed synovium of a synovial joint of a

person suffering from inflammatory arthropy, such as rheumatoid arthritis. It comprises a radionuclide or radionuclide complex bound to a substantially insoluble particle as the radiation synovectomy agent in a sufficient amount to provide satisfactory synovectomy when administered with a pharmaceutically acceptable radiation synovectomy vehicle. The radionuclide is a beta emitter that would substantially ablate or destroy the diseased synovium, but will not significantly damage underlying articular cartilages or overlying skin. The radionuclide complex is substantially kinetically stable, but should degradation lead to leakage from the joint after administration, the radioactive material will rapidly clear from the body. A substantially kinetically stable complex as known to those skilled in the art is a complex which under normal biological conditions is kinetically stable, but not necessarily 100 percent kinetically stable in each and every patient application since biological systems vary somewhat. However, the necessary stability of the complex is determinant upon the half-life of the radioisotope being used. After the isotope has decayed to the point of being insignificant, the stability of the complex is no longer important. The particle size of the agent is of sufficient size such that there is essentially little or no leakage of the intact radionuclide complex-particle unit from the synovial joint after administration. Additionally, the size and properties of the particle can be defined and controlled before it is bound to the radionuclide complex resulting in an agent having good synovectomy properties. Also, the binding of the radionuclide complex can be controlled resulting in better reproductivity and more complete binding and better in vivo clearance.

As mentioned, the radiation agent comprises a substantially insoluble particle which is of suitable size as to not substantially leak from the joint after administration. Normally, the size may be from approximately 0.5 to 40 microns. These particles are preferably biodegradable (but can also be degradable by other mechanisms) and not prone to aggregation under the

conditions used to prepare or store the radiation synovectomy agent. The particle should have a density of approximately 0.7 to 3.5 gm/ml, preferably from 0.7 to 2.0 gm/ml, and should be suspendable in pharmaceutically acceptable vehicles. Some of the material from which such particles can be made include latex, derivatized polystyrene, silica, alumina, albumin (such as albumin microspheres), other proteins, polycarbonates, cellulose and inorganics, e.g., sulfur (colloid) glass (beads), hydroxyapatites, calcium phosphates or calcium pyrophosphates. For purposes of this application, the term "hydroxyapatite(s)" shall include materials known as hydroxyapatite(s) and also as hydroxylapatite(s). These two terms have been used previously in the literature to refer to the same materials. Examples of hydroxyapatites for this application include matrix prepared from the bones and or teeth of animals and matrix prepared by inorganic synthesis, each being more amorphous than crystalline in composition. This includes calcium-hydroxy-hexaphosphate ($3(Ca_3(PO_4)2)Ca(OH)_2$; also given as $2[Ca_5(PO_4)_3OH]$). The particles have sites on the surface that permit absorption or covalent binding of the radionuclide or radionuclide complex. Such sites can include but are not limited to $-NH_2$, -SH, -OH, >C=O, calcium, hydroxyl, phosphate and similar such sites, and hydrophobic or hydrophilic regions or pockets. In addition to being insoluble, the particles must be non-toxic and preferably non-allergenic. Preferred particles include albumin microspheres, sulfur colloid, hydroxyapatite and hydroxyapatite-like matrix.

As used herein, apatite particles include apatite-like minerals of the general formula $Ca_nM_mX_rY_s$, where M is a paramagnetic metal ion or stoichiometric mixture of metal ions having a valence of 2+ or 3+, X is a simple anion, Y is a tetrahedral oxyanion, carbonate, tetrahedral anion, or mixtures thereof, m is from 1-10, n is from 1-10, and r and s are adjusted as needed to provide charge neutrality. Where M is a 2+ metal ion, then m + n =

10, and where M is a 3+ metal ion, then m + 1.5n = 10.

Thus, the invention comprises a composition comprising an apatite particle having the following general formula:

$$Z\text{-}Ca_nM_mX_rY_s$$

wherein M is a paramagnetic ion or stoichiometric mixture of metal ions having a valence of 2+ or 3+, X is a simple anion, Y is a tetrahedral oxyanion, carbonate, tetrahedral anion, or mixtures thereof, m is from 1-10, n is from 1-10, where M is a 2+ metal ion, then m + n = 10, and where M is a 3+ metal ion, then m + 1.5n = 10, r and s are adjusted as needed to provide charge neutrality, and Z is a β-emitting radionuclide(carrier-free or carrier-added).

Possible metal ions which can be used in the apatite particles of the present invention include: chromium(III), manganese(II), iron(II), iron(III), praseodymium(III), neodymium(III), samarium(III), ytterbium(III), gadolinium(III), terbium(III), dysprosium(III), holmium(III), erbium(III), or mixtures of these with each other or with alkali or alkaline earth metals. Typical simple anions which can be used in the apatite particles of the present invention include: OH^-, F^-, Br^- I^-, $½[CO_3^{2-}]$, or mixtures thereof.

The paramagnetic metal species is incorporated into the apatite particles to improve magnetic resonance contrast. The apatite particles may also be fluorinated to form stable, nontoxic fluoroapatite compositions useful for ^{19}F imaging. The presence of a paramagnetic metal species in fluoroapatite or hydroxyapatite particles may reduce ^{19}F and proton relaxivity, thereby enhancing MRI, MRS, or MRSI.

Preparation of Apatite Particles

Methods for preparing hydroxyapatite, having the formula $Ca_{10}(PO_4)_6(OH)_2$, are well known in the art. Apatites in which the OH^- is

replaced with simple anions, including F^-, Br^-, I^-, or $\frac{1}{2}[CO_3^{2-}]$, may be prepared by modifying the process for preparing hydroxyapatite. Apatite derivatives in which calcium is replaced by a paramagnetic metal ion may also be prepared and used within the scope of the present invention.

Stoichiometric pure hydroxyapatite has a Ca:P ratio of 1.67:1. The major impurity found in hydroxyapatite is tricalcium phosphate, $Ca_3(PO_4)_2$, known as "TCP". This impurity can be detected by deviation from the 1.67:1 Ca:P ratio (for large amounts of impurity) or by X-ray diffraction for impurity levels down to 1 percent.

Stoichiometric hydroxyapatite is prepared by adding an ammonium phosphate solution to a solution of calcium/ammonium hydroxide. To minimize the amount of TCP formed, it is important to have excess calcium throughout the addition process.

Apatite Particles for MRI Applications

The technique of MRI encompasses the detection of certain atomic nuclei (those possessing magnetic dipole moments) utilizing magnetic fields and radio-frequency radiation. It is similar in some respects to X-ray computed tomography ("CT") in providing a cross-sectional display of the body organ anatomy with excellent resolution of soft tissue detail. The technique of MRI advantageously avoids the use of ionizing radiation.

The hydrogen atom, having a nucleus consisting of a single unpaired proton, has the strongest magnetic dipole moment of any nucleus. Since hydrogen occurs in both water and lipids, it is abundant in the human body. Therefore, MRI is most commonly used to produce images based upon the distribution density of protons and/or the relaxation times of protons in organs and tissues. Other nuclei having a net magnetic dipole moment also exhibit a nuclear magnetic resonance phenomenon which may be used in magnetic resonance applications. Such nuclei include carbon-13 (six protons

and seven neutrons), fluorine-19 (9 protons and 10 neutrons), sodium-23 (11 protons and 12 neutrons), and phosphorus-31 (15 protons and 16 neutrons).

In an MRI experiment, the nuclei under study in a sample (e.g. protons, ^{19}F, etc.) are irradiated with the appropriate radio-frequency ("RF") energy in a controlled gradient magnetic field. These nuclei, as they relax, subsequently emit RF energy at a sharp resonance frequency. The resonance frequency of the nuclei depends on the applied magnetic field.

According to known principles, nuclei with appropriate spin when placed in an applied magnetic field (B, expressed generally in units of gauss or Tesla (10^4 gauss)) align in the direction of the field. In the case of protons, these nuclei precess at a frequency, F, of 42.6 MHz at a field strength of 1 Tesla. At this frequency, an RF pulse of radiation will excite the nuclei and can be considered to tip the net magnetization out of the field direction, the extend of this rotation being determined by the pulse, duration and energy. After the RF pulse, the nuclei "relax" or return to equilibrium with the magnetic field, emitting radiation at the resonant frequency. The decay of the emitted radiation is characterized by two relaxation times, T_1 and T_2. T_1 is the spin-lattice relaxation time or longitudinal relaxation time, that is, the time taken by the nuclei to return to equilibrium along the direction of the externally applied magnetic field. T_2 is the spin-spin relaxation time associated with the dephasing of the initially coherent precession of individual proton spins. These relaxation times have been established for various fluids, organs, and tissues in different species of mammals.

For protons and other suitable nuclei, the relaxation times T_1 and T_2 are influenced by the environment of the nuclei (e.g., viscosity, temperature, and the like). These two relaxation phenomena are essentially mechanisms whereby the initially imparted radio-frequency energy is dissipated to the surrounding environment. The rate of this energy loss or relaxation can be

influenced by certain other nuclei or molecules (such as nitroxide radicals) which are paramagnetic. Chemical compounds incorporating paramagnetic nuclei or molecules may substantially alter the T_1 and T_2 values for nearby nuclei having a magnetic dipole moment. The extent of the paramagnetic effect of the given chemical compound is a function of the environment within which it finds itself.

In general, paramagnetic ions of elements with an atomic number of 21 to 29, 42 to 44 and 58 to 70 have been found effective as MRI contrasting agents. Examples of suitable paramagnetic ions include chromium(III), manganese(II), iron(II), iron(III), cobalt(II), nickel(II), copper(II), praseodymium(III), neodymium(III), samarium(III), gadolinium(III), dysprosium(III), and ytterbium(III). Certain molecules, such as nitroxide radicals, also exhibit paramagnetic properties.

Paramagnetic metal ions may be incorporated into the apatite structure by replacement of calcium sites. Apatite doping in the range from about 1% to 100% is possible, depending upon the particular metal species. In most cases, apatite doping with metal ions in the range from about 1% to 25% is expected. Currently, the preferred metals from a toxicity and efficacy viewpoint are iron and manganese. With iron doped hydroxyapatite particles, any iron released from metabolized or solubilized particles would join the body's pool of iron, with calcium and phosphate also going to their respective body pools. Manganese is preferred because of its higher relaxivity properties and affinity for liver tissue. Moreover, the liver has a clearance mechanism for manganese, thereby reducing residual toxicity.

Metal doped hydroxyapatite is prepared by mixing a basic (pH 12) phosphate solution with a calcium/paramagnetic metal solution at native pH. Alternatively, the calcium/paramagnetic metal solution could be basic (pH 12) if the solution also contains a ligand to prevent hydrolysis of the paramagnetic

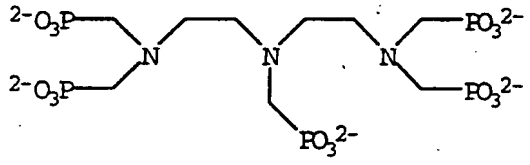
metal. The ligand could either be left in the hydroxyapatite matrix or "ashed out" by sintering the hydroxyapatite between 200°C and 1100°C. Any strong chelating ligands may be used, such as polyamino polycarboxylic acid derivatives which are well known in the art.

It has been found that the paramagnetic ions incorporated into the apatite particle tend to oxidize during particle synthesis. To prevent metal oxidation, manufacturing techniques have been developed to minimize the amount of oxygen in the aqueous reactant solutions. For example, two such manufacturing techniques are (1) synthesis at high temperature, such as 100°C and (2) degassing the aqueous reactant solutions with an inert gas such as argon, nitrogen, or helium. An unexpected benefit of these techniques is the ability to prepare smaller particles, in the range from 50 nm to about 1 μm.

Antioxidants, such as gentisic acid and ascorbic acid, added during apatite particle synthesis may also be used to prevent metal ion oxidation. Reducing agents, such as $NaBH_4$, have been found to reduce metal ions that are unintentionally oxidized during apatite particle synthesis.

Paramagnetic apatite particles may also be prepared by adsorbing paramagnetic metal ions onto the particle surface. For example, manganese can be surface-adsorbed to hydroxyapatite particles by taking a slurry of hydroxyapatite, adding $Mn(NO_3)_2$ and applying energy, such as ultrasonic power or heat, to the resulting mixture. The resulting mixture can be separated by either centrifugation and decantation or by filtration. The resulting solid is washed with large amounts of water to remove excess manganese. The same procedure may be used with other paramagnetic cations. The amount of manganese adsorbed onto the particle surface, as a percentage of the total calcium in the particle, is in the range from about 0.1% to about 10%. Such particles exhibit very high relaxivities and rapid liver enhancement in magnetic resonance imaging studies.

Paramagnetic metal species may also be adsorbed onto apatite particle surfaces through the use of bifunctional coating agents. Examples of possible bifunctional coating agents are chelating agents having one or more phosphonate groups capable of adsorption to the apatite particle surface. One currently preferred bifunctional coating agent is the functionalized polyphosphonate diethylenetri-aminepenta(methylenephosphonic acid), abbreviated DETAPMDP, having the following structure:



Once adsorbed to the apatite particle surface, the bifunctional coating agent may form complexes with paramagnetic metal ions. These particles also exhibit very high relaxivities and rapid liver enhancement in magnetic resonance imaging studies.

In some cases, the concentration of nuclei to be measured is not sufficiently high to produce a detectable MR signal. For instance, since ^{19}F is present in the body in very low concentration, a fluorine source must be administered to a subject to obtain a measurable MR signal. Signal sensitivity is improved by administering higher concentrations of fluorine or by coupling the fluorine to a suitable "probe" which will concentrate in the body tissues of interest. High fluorine concentration must be balanced against increased tissue toxicity. It is also currently believed that a fluorine agent should desirably contain magnetically equivalent fluorine atoms in order to obtain a clear, strong signal.

Fluoroapatites, useful as ^{19}F imaging agents, are prepared by replacing

the OH^- with stoichiometric or non-stoichiometric quantities of F^-. Fluoroapatites may also be synthesized with organic phosphate esters using the procedures described by M. Okazaki, "Fluoridated Hydroxyapatites Synthesized With Organic Phosphate Ester," Biomaterials, Vol. 12, pp. 46-49, (1991). It is currently believed that all of the fluorine atoms in fluoroapatite are chemically and magnetically equivalent. Since fluoroapatite has a high molar content of identical fluorine atoms, it may be advantageously used as a low concentration ^{19}F MRI agent. Fluoroapatite may also be doped with paramagnetic metal species, as described above, to reduce ^{19}F and proton relaxivity, thereby enhancing MRI, MRS, or MRSI.

Controlling the Particle Size and Aggregation

Various techniques are available to control the apatite particle size. For example, slower mixing rates (introduction of the precipitating anion or cation), larger solution volumes, higher reaction temperatures, and lower concentrations generally result in smaller particles. In addition, sonication during precipitation, turbulent flow or impingement mixers, homogenization, and pH modification may be used to control particle size.

Procedures for preparing monodispersed colloidal particles that are known in the art may be adapted for preparing submicron apatite particles. E. Matijević, "Production of Monodispersed Colloidal Particles," Annual Review of Material Science, volume 15, pages 483-516, 1985, which is incorporated herein by reference, describes methods for controlling the release of precipitating anions and cations. For example, when urea, $CO(NH_2)_2$, is heated, hydroxide ions are slowly liberated which can cause precipitation of hydroxyapatite as submicron particles. Likewise, precipitating cations can be released slowly by decomposition of metal complexes, such as organometallic compounds.

In addition to chemical means for controlling the release of precipitating

ions, mechanical means, such as computer controlled autoburets, peristaltic pumps, and syringes, may also be used to control the release of precipitating ions. Commercially available autoburets are capable of releasing solutions at rates as low as 10 μL/minute. In the future as computer controlled equipment improves, it is expected that even slower release rates may be obtained.

Due to the small size and nature of apatite particles, they tend to aggregate. Particle aggregation may be reduced by coating the particles. Although the reasons apatite particles aggregate is not fully understood, it has been found that several different coating agents are able to inhibit particle aggregation. For example, apatite particles may be stabilized by treatment with coating agents such as di- and polyphosphonate-containing compounds, such as hydroxyethyldiphosphonate (HEDP), pyrophosphate, aminophosphonates; carboxylates and polycarboxylate-containing compounds such as oxalates and citrates; alcohols and polyalcohol-containing compounds; phosphates and polyphosphate-containing compounds; sulfates and sulfate-containing compounds; sulfonates and sulfonate-containing compounds; and biomolecules such as peptides, proteins, antibodies, and lipids. Such coating agents stabilize the small apatite particles by reducing further particle growth and promoting particle suspension.

Stabilized apatite particles are desirable for <u>in vivo</u> use as medical diagnostic imaging agents. Apatite particle can also be stabilized by addition of small amounts of calcium sequestering anions, such as citrate and oxalate. Such anions, which coordinate calcium, may effectively stabilize small apatite particles.

When used in magnetic resonance imaging, particle relaxivity is enhanced by allowing more water accessible to the particle surface. By limiting particle size and increasing the available surface area, improved relaxivity is observed.

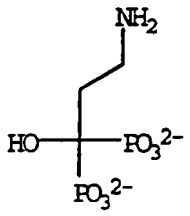
In addition to the coating agents identified above, conventional particle coating techniques may also be used in the manufacturing processes of the present invention. Typical coating techniques are identified in International Publication Numbers WO 85/02772, WO 91/02811, and European Publication Number EP 0343934, which are incorporated by reference.

For instance, agglomerated particles may be disrupted by mechanical or chemical means and then coated with polymers such as carbohydrates, proteins, and synthetic polymers. Dextran having a molecular weight in the range from about 10,000 to about 40,000 is one currently preferred coating material. Albumin and surfactants, such as tween 80, have also been used to reduce particle aggregation. One common characteristic of useful apatite coating agents is their ability to modify the particle surface charge, or zeta potential.

The currently preferred mechanical means for disrupting or subdividing agglomerated particles is sonication, but other means such as heating, other forms of particle energization, such as irradiation, and chemical means, such as pH modification or combinations of these types of treatment, such as pH modification combined with sonication may be used.

Functionalized Apatite Particles

Apatite particles may be prepared with coating agents containing reactive functional groups such as amine, active ester, alcohol, and carboxylate. Polyethylene glycols (PEG) and derivatized PEG's may also be used as coating agents. Such functional groups may be used to couple apatite particles to paramagnetic metal chelates, to organ or tissue specific peptides or proteins, and to antibodies. An example of one possible coating agent having a reactive functional group is the following HEDP derivative:



Those skilled in the art will appreciate that other coating agents, modified to contain various reactive functional groups, may be used in the present invention.

When using hydroxyapatite or hydroxyapatite-like matrix, the particle size thereof becomes important. This is because of reports that hydroxyapatite particles may become phagocytosed and solubilized by synovial fibroblasts. In particular, it is believed that the hydroxyapatite particles are first solubilized by phagocytosis and then dissolved in the acidic environment of secondary lyposomes.

Therefore, it is necessary to establish means to maintain the hydroxyapatite of the radiation synovectomy agent for an effective period of time in the synovial cavity. In particular, the rate of solubilization of the hydroxyapatite should optimally be much slower than the half-life of the radioisotope used in the radiation synovectomy agent. In this manner, the radioisotope may completely decay before dissolution of the hydroxyapatite particle. It has been determined that the rate of solubilization and dissolution of hydroxyapatite is a function of particle size, wherein smaller particles are more quickly phagocytosed and dissolved than larger particles. Studies have suprisingly shown that there is no significant lower limit on particle size. In particular, there have been no problems associated with leakage regardless of particle size. For practicle purposes, a particle size of 0.5 microns or greater is preferred, however, smaller particle sizes would be acceptable. It is believed

that this is because of the relatively high charge of hydroxyapatite and the tendency of hydroxyapatite particles to aggregate.

Maximum particle size is approximately 40 microns. If particles are too large, e.g. greater than 40 microns, the particles can not be surrounded by cells and will not be easily phagocytosed and dissolved. This can disadvantagously cause dead fibrous areas too occur in the synovium.

In light of the above, when using hydroxyapatite particles as the particles of the radiation synovectomy agent according to the present invention, it is desirable that the hydroxyapatite particles have a particle size of 0.5 to 40 microns.

The radioisotopes that can be used are those that emit beta particles and are such that after administration will ablate the diseased synovium but will not significantly damage the underlying articular cartilage or overlying skin. These isotopes should have an average beta energy between 0.25 - 2.75 Mev, with or without an imageable gamma ray, with mean soft tissue penetration of about 0.70 and 25.0 mm, and with a half-life of between 0.05 and 700 hours. Examples of preferred beta emitting isotopes include 198-Au, 188-Re, 186-Re, 177-Lu, 176m-Lu, 175-Yb, 169-Er, 166-Ho, 165-Dy, 156-Sm, 153-Sm, 115m-In, 105-Rh, 90-Y, 51-Cr, 77-As, 67-Cu and 32-P, in addition to others of the lanthanide group such as, 141-Ce, 144-Pr, 147-Nd, 148-Pm, 152-Eu, 153-Gd, 157-Tb and 170-Tm. Preferably the isotope would either have an imageable gamma ray or could be doped with an isotope that would contain an imageable gamma ray. This doping isotope could be of the same or different element providing that its chemistry is sufficiently similar to the beta emitting isotope so that its biodistribution in the present use would be close or identical to the beta emitter. Preferred isotopes include: 186-Re, 188-Re, 90-Y, 153-Sm, 77-As, 105-Rh, 177-Lu, 176m-Lu and 166-Ho.

The radionuclide complexes that can be used are those that are stable

before and after administration to the synovium joint. Additionally, if such complex leaks from the joint it will be rapidly cleared from the body. This will be the case even if the complex becomes separated from the insoluble particle. The complexes are formed by complexing the radionuclide under complexing conditions with a suitable ligand to provide a complex with the foregoing properties. Ligands that can be used are preferably polydentate, i.e., containing more than two coordinating atoms per ligand molecule. A coordinating atom is defined as one that has a free pair of electrons which can be bonded to the radionuclide. This atom is preferably separated by two or more atoms from any other coordinating atom. The coordinating atoms are chosen from nitrogen, oxygen, sulfur, phosphorus or carbon with nitrogen and/or oxygen and/or sulfur being the preferred coordinating atoms. Examples of chelates include all phosphonate carboxylate and amine carboxylate ligands, citrate, MAG_3 (mercaptoacetylglycylglycylglycine), all polycarboxylic acid-amine ligands especially DTPA (diethylenetri-aminepentaacetic acid), e.g., EDTA (ethylenediamine-tetraacetic acid), DADS (N,N'-bis(mercaptoacetamido)-ethylenediamine and CO_2-DADS N,N'-bis(mercaptoacetamido)-2,3-diaminopropanoic acid) and their derivatives (see European Application 0173424 and US Patent 4,673,562), mono- and poly-phosphonates, BATs (N,N'-bis(2-mercapto-ethyl)ethylene-diamine) and derivatives (see European Applications 0163119 and 0200211), thiosemicarbazones, PnAO and other amine-oxime ligands (See European Applications 0123504 and 0194843), marcocyclic and open chain tetra-, penta-, hexa-, hepta- and octacoordinating nitrogen-containing compounds with or without other coordinating atoms or unsaturation. Examples of preferred phosphonate ligands include but are not limited to those specified in U.S. Patents Numbered 4,234,562; 3,983,227; 4,497,744; 4,233,284; 4,232,000; 4,229,427; and 4,504,463; preferably HEDP (hydroxyethyldiphosphonate), PYP

(pyrophosphate), EDTMP (ethylenediaminetetramethylphosphate), and HMDP (hydroxymethylenediphosphonate).

Other ligands include MAG_3, DTPA, BAT, DADS and PnAO type ligands which have been modified so that they are bifunctional, i.e., can coordinate the radionuclide and also be coupled to the particle. Preferred complexes include a citrate/hydroxyapatite or hydroxyapatite-like matrix complexed with 186-Re, 188-Re, 105-Rh, 153-Sm or 156-Sm.

The composition of this invention can be prepared by attaching or binding to the paramagnetic-containing particle the desired isotope under standard conditions for attachment. This involves coupling a ligand (either with or without a radioactive atom) to the particle with or without the presence of a spacer between the two units. Generally, the coupling can be done by any group(s) attached to the ligand that is (are) not crucial for complexing the radioisotope in a stable manner. This coupling portion of the ligand may consist of any group that can easily and specifically bind covalently to functional groups on the particle or that may simply adsorb very strongly to the surface of the particle. Examples of the covalent coupling would include amino-carboxylate, carboxylate or phosphonate ligands which would combine with Ca^{2+} at or near the surface of the particle, activated esters of carboxylic acids which would combine covalently to amine groups, to sylates and acid halides which would combine with OH groups and maleimides which would combine with thiol groups, with the thiol, amine and OH groups assumed to be at or near the surface of the particle.

The following methods of preparing the desired radiation synovectomy agent may be used:

(a) The pre-formed method: One of the previously described radionuclide complexes is covalently bonded to one of the previously described particles having functional groups. Step one - a particle of the

optimal size, (e.g., 1-10 microns, 5-50 microns) and composition (e.g., hydroxyapatite, hydroxyapatite-like matrix, albumin, polycarbonate, cellulose, glass, latex) and having appropriate residues (amines, hydroxyls, hydroxide, phosphate, carboxylates, thiols) is selected. Step two - a radioisotope (of the appropriate nuclear characteristics) which has been incorporated into a ligand (i.e., a radionuclide complex) is covalently bonded to the particle.

(b) The post-formed method: A ligand is covalently bonded to one of the previously described particles. Thereafter, one of the previously described radioisotopes is incorporated into the covalently bonded complexing ligand, after the radionuclide has been treated in such a way, e.g., using a transfer ligand such as citrate or tartarate to facilitate transfer of the radionuclide to the ligand, to make it bind more readily to the ligand.

The compositions of this invention may be used in any pharmaceutically acceptable vehicle. These include those suitable for injection, such as aqueous buffer solutions, e.g., (trishydroxymethyl)aminomethane and its salts, phosphate, citrate, bicarbonate, e.g., sterile water for injection, physiological saline and balanced ionic solutions containing chloride and/or bicarbonate salts of normal blood plasma cations such as calcium, sodium, potassium, magnesium. Other buffer solutions are described in Remington's Practice of Pharmacy, 11th Edition, for example on page 170. Additionally, the vehicle may contain stabilizers, antioxidants and other adjuncts. Stabilizers include gelatin or other materials in stabilizing amounts to prevent aggregation of the particles, antioxidants in antioxidant amounts such as reducing sugars (e.g., fructose, or free acid or metal salts of gentisic acid) ascorbic acid and other adjuvants such as reducing agents, preferably stannous salts, intermediate exchange ligands in exchange amounts such as metal salts of tartrate, gluconate or citrate as well as bulking agents in bulking amounts such as lactose.

The composition may be formulated in a one-step procedure as a lyophilized kit where the radioisotope solution is injected for reconstitution or as an autoclaved or radiation sterilized solution which is then treated with the radioisotope. In this case, the ligand has already been attached to the paramagnetic-containing particle before lyophilization or autoclaving. The product may be formulated in a two-step scheme where the radioisotope is bound to the ligand and then this complex with or without purification as necessary is combined with the paramagnetic-containing particles to give the final composition. Any of these steps may require heating and any of the intermediates or final products may require purification before use.

The radiolabeled, paramagnetic-containing apatite particles of this invention are preferably formulated for parenteral administration. For example, parenteral formulations advantageously contain a sterile aqueous solution or suspension of treated apatite particles according to this invention. Various techniques for preparing suitable pharmaceutical solutions and suspensions are known in the art. Parenteral compositions may be injected directly or mixed with a large volume parenteral composition for systemic administration.

The compositions of this invention are used in a conventional manner with regard to its magnetic resonance imaging applications. The compositions are administered in a sufficient amount to provide adequate visualization, to a warm-blooded animal by direct injection into the joint to be treated and imaged, then the animal is subjected to the MRI procedure. Such doses may vary widely, but are readily determined by one of ordinary skill in the art. The amount of the radionuclide in the pharmaceutically acceptable vehicle also varies with the particular use. A sufficient amount is present to provide satisfactory radiation synovectomy. This amount will vary with the physical properties of the isotope being used. For example, when using 186-Re for

radiation synovectomy of the hip, a sufficient amount is 2 to 5 mCi and preferably from 3 to 4 mCi. When it is used for the radiation synovectomy of the wrist joints, it is used in an amount from 1 to 3 mCi and preferably from 1 to 2 mCi. When using 153-Sm for radiation synovectomy of the knee, the amount used is approximately 10-20 mCi.

The composition is administered so that preferably it remains substantially in the joint for 20 half-lifes of the isotope although shorter residence times are acceptable as long as the leakage of the radionuclide is small and the leaked radionuclide is rapidly cleared from the body.

The compositions may be used in the usual way for radiation synovectomy procedures. For example, in the case of the treatment of a knee-joint, a sufficient amount of the radiation synovectomy composition to provide adequate radiation synovectomy is injected into the synovial cavity of the knee. There are a number of different techniques which can be used and the appropriate technique varies on the joint being treated. An example for the knee joint has been excerpted below from Nuclear Medicine Therapy, J.C. Harbert, J.S. Robertson and K.D. Reid, 1987, Thieme Medical Publishers, pages 172-3.

Strict asepsis is essential. The area to be aspirated and/or injected should be cleansed and prepped as for a spinal tap.

The injection site is selected by first obtaining radiographs in two planes with the joint position at the injection angle. These are used to correlate easily palpable bony landmarks as a guide for needle placement. Major nerves, vessels and tendons should be avoided. Extensor surfaces are the preferred injection sites. The specific area of the joint to be injected is then marked with firm pressure by a ballpoint pen which has the writing tip retracted. This will leave an impression lasting 10 to 30 minutes. The area is carefully cleansed with Betadine solution and the injection site is anesthetized with 1% xylocaine.

The injection needle is then inserted through the ballpoint impression, using care to avoid hitting the cartilage. Following insertion, the needle position may be checked by MRI contrast imaging. The joint is then imaged to assure distribution throughout the joint space. This is an important precaution, because loculated distribution is probably a common cause of treatment failure. The joint is then splinted or the patient confined to bed rest for 48 hours to minimize leakage from the joint space (in the case of ^{165}Dy-macroaggregates, 7 hours bed rest is deemed sufficient.)

The knee is the easiest joint to inject. The patient should be in a supine position with the knee fully extended. The puncture is made 1 to 2 cm medial to the medial margin of the patella using an 18-gauge by 1.5 in. needle directed slightly inferiorly and toward the joint space. The joint space should be entered and easily aspirated. If osteophytes make this approach difficult, the knee may be injected with the patient sitting and the knee fixed. In this case, the needle is placed beneath the distal border of the patella and directed straight posteriorly or slightly superiorly toward the joint cavity.

In most cases after the joint has been injected, it is either (1) moved to allow homogeneous distribution of the radiation synovectomy agent and then immobilized and shielded with appropriate radioactive shielding for a period of time related to the half-life of the isotope or (2) simply immobilized and shielded without working the joint.

The following examples are offered to further illustrate the present invention. These examples are intended to be purely exemplary and should not be viewed as a limitation on any claimed embodiment.

Example 1

Preparation of Hydroxyapatite

A calcium nitrate solution was prepared by adding 1.18 g

$Ca(NO_3)_2 \cdot 4H_2O$ to 20 mL deionized water such that the final $[Ca^{2+}]$=0.25 M. The calcium nitrate solution pH was adjusted to a pH of 11 with ammonium hydroxide. An ammonium phosphate solution was prepared by adding 0.396 g $(NH_4)_2HPO_4$ to 5 mL of deionized water. The pH of the ammonium phosphate solution was adjusted to a pH of 11 with ammonium hydroxide. The ammonium phosphate solution was injected into the calcium nitrate solution and vigorously stirred. The resulting precipitated particles were examined under a microscope and estimated to have particle sizes greater than 10 μm.

Example 2

Preparation of Hydroxyapatite

Hydroxyapatite particles were prepared according to the procedure of Example 1, except that the pH of the calcium nitrate solution was not adjusted to pH 11. The ammonium phosphate solution was injected into the calcium nitrate solution and vigorously stirred. The resulting precipitated particles were examined under a microscope and estimated to have particle sizes greater than 10 μm.

Example 3

Preparation of Hydroxyapatite

A calcium nitrate solution was prepared by adding 0.68 g $Ca(NO_3)_2 \cdot 4H_2O$ to 5 mL deionized water such that the $[Ca^{2+}]$=0.58 M. The calcium nitrate solution pH was adjusted to a pH of 11 with ammonium hydroxide. An ammonium phosphate solution was prepared by adding 0.22 g $(NH_4)_2HPO_4$ to 10 mL of deionized water such that the $[HPO_4^{2-}]$=0.17 M. The pH of the ammonium phosphate solution was adjusted to 11 with ammonium

hydroxide. The ammonium phosphate solution was dripped into a vigorously stirred calcium nitrate solution over 30 minutes. After mixing, the final $[Ca^{2+}]$=0.19 M. The resulting precipitated particles were examined under a microscope and estimated to have particle sizes of approximately 1 μm.

Example 4

Preparation of Hydroxyapatite Doped with a Paramagnetic Metal Ion

A metal ion solution was prepared by adding 1.18 g $Ca(NO_3)_2 \cdot 4H_2O$ and 0.202 g $Fe(NO_3)_3 \cdot 9H_2O$ to 20 mL deionized water. An ammonium phosphate solution was prepared by adding 0.396 g $(NH_4)_2HPO_4$ to 5 mL of deionized water. The pH of the ammonium phosphate solution was adjusted to 11 with ammonium hydroxide. The ammonium phosphate solution was injected into the metal ion solution and vigorously stirred. The resulting precipitated particles were examined and found to have particle sizes greater than 10 μm.

Example 5

Preparation of Fluoroapatite

Fluoroapatite is prepared by mixing 5 mL of a 0.58 M solution of calcium fluoride with 10 mL of a 0.17 M ammonium phosphate solution at native pH. The calcium fluoride solution is dripped into a vigorously stirred ammonium phosphate solution over 30 minutes. The resulting precipitated particles are examined under a microscope and estimated to have particle sizes of approximately 1 μm.

Example 6

Preparation of Fluoroapatite

Fluoroapatite is prepared by mixing 5 mL of a 0.58 M solution of calcium nitrate with 10 mL of solution containing 0.17 M ammonium phosphate and 0.17 M ammonium fluoride. The calcium nitrate solution is dripped into a vigorously stirred ammonium phosphate and ammonium fluoride solution over 30 minutes. The resulting precipitated particles are examined under a microscope and estimated to have particle sizes of approximately 1 μm.

Example 7

Preparation of Fluoroapatite Doped with a Paramagnetic Metal Ion

Fluoroapatite doped with a paramagnetic metal ion is prepared according to the procedure of Example 5, except that the calcium fluoride solution also contains 0.058 M manganese nitrate. The calcium fluoride/manganese nitrate solution is dripped into a vigorously stirred ammonium phosphate solution over 30 minutes. The resulting precipitated particles are examined under a microscope and estimated to have particle sizes of approximately 1 μm.

Example 8

Preparation of Iodoapatite

Iodoapatite is prepared by mixing 5 mL of a 0.58 M solution of calcium iodide with 10 mL of a 0.17 M ammonium phosphate solution at native pH. The calcium iodide solution is dripped into a vigorously stirred ammonium phosphate solution over 30 minutes. The resulting precipitated particles are examined under a microscope and estimated to have particle sizes of approximately 1 μm.

Example 9

Preparation of Iodoapatite

Iodoapatite is prepared by mixing 5 mL of a 0.58 M solution of calcium nitrate with 10 mL of solution containing 0.17 M ammonium phosphate and 0.17 M ammonium iodide. The calcium nitrate solution is dripped into a vigorously stirred ammonium phosphate and ammonium iodide solution over 30 minutes. The resulting precipitated particles are examined under a microscope and estimated to have particle sizes of approximately 1 μm.

Example 10

Preparation of Hydroxyapatite Doped with Carbonate

Carbonate-doped hydroxyapatite particles are prepared according to the procedure of Example 3, except that calcium carbonate was used instead of calcium nitrate. The ammonium phosphate solution is dripped using a computer controlled autoburet into a vigorously stirred calcium carbonate solution over 30 minutes. The resulting precipitated particles were examined under a microscope and estimated to have submicron particle sizes.

Example 11

Preparation at 100°C of Hydroxyapatite

An ammonium phosphate solution was prepared by dissolving 10.56 grams $(NH_4)_2HPO_4$ in 200 mL of D.I. water. To this was added 100 mL of concentrated NH_4OH with stirring. A white precipitate formed which was dissolved by addition of 150 mL of H_2O. This solution was stirred for 3 hours at room temperature and then added dropwise (over 2 hours) via a peristaltic pump (Masterflex) to a 1000 mL three-neck round bottom flask fitted with a dry ice/ isopropanol condenser on top of a standard water-jacketed condenser

containing a solution of 31.5 grams $Ca(NO_3)_2 \cdot 4H_2O$ in 500 mL of H_2O in boiling water stirred rapidly with a mechanical stirrer. Reflux was continued for two hours after addition was complete and the mixture was allowed to cool to room temperature with stirring overnight. The reaction mixture was centrifuged at 2300 rpm and the nearly-clear supernatant discarded. The resulting white, pelleted solid was slurried with water and completely broken up by means of a vortex mixer. The mixture was again centrifuged and the cloudy supernatant collected. The washing was repeated two separate times. All three washings were saved as was the remaining solid in the centrifuge tubes. The calcium/phosphorous ratio and particle size of the washed particles is summarized below:

	Ca/P Ratio	Particle size (std. dev.)
wash 1:	1.65	663 (456) nm
wash 2:	1.67	351 nm, 1853 nm†
wash 3:	1.67	190 nm, 1069 nm†

†Bimodal distribution noted, no standard deviations given.

Example 12

Preparation at 100°C of Hydroxyapatite Doped with Mn(II)

This material was prepared according to the procedure of Example 11 except that a Mn(II) (as $Mn(NO_3)_2 \cdot H_2O$) was substituted mole-for-mole for Ca. For example, to synthesize 5% Mn incorporated into HA:

10.56 grams $(NH_4)_2HPO_4$ was dissolved in 200 mL of D.I. water. To this was added 100 mL of concentrated NH_4OH with stirring. A white precipitate formed which was dissolved by addition of 150 mL of H_2O. This solution was stirred for 3 hours at room temperature and then added dropwise (over 2 hours) via a peristaltic pump (Masterflex) to a 1000 mL three-neck round

bottom flask fitted with a dry ice/ isopropanol condenser on top of a standard water-jacketed condenser containing a solution of 1.27 grams $Mn(NO_3)_2 \cdot H_2O$ and 29.9 grams $Ca(NO_3)_2 \cdot 4H_2O$ in 500 mL of H_2O in boiling water stirred rapidly with a mechanical stirrer. Reflux was continued for two hours after addition was complete and the mixture was allowed to cool to room temperature with stirring overnight. The reaction mixture was centrifuged at 2300 rpm and the nearly-clear supernatant discarded. The resulting off-white, pelleted solid was slurried with water and completely broken up by means of a vortex mixer. The mixture was again centrifuged and the cloudy supernatant collected. The washing procedure was repeated two times. All three washings were saved as was the remaining solid in the centrifuge tubes. The particle size of the particles in the supernatant increased and the percentage of particles in the supernatant decreased (i.e., less cloudy supernatant). Solids from supernatants could be concentrated by further centrifugation at 7000 rpm. The average particle size was 449 nm with a standard deviation of 171 nm.

Example 13

Preparation at 100°C of Hydroxyapatite particles Doped with Mn and treated with HEDP

Manganese containing hydroxyapatite particles were prepared by the following general procedure (Mn/Ca mole ratios of < 0.33 can be used):

A solution containing 6.5 g of $(NH_4)_2HPO_4$ in 120 mL of deionized water was treated with 60 mL of concentrated ammonium hydroxide, NH_4OH followed by 90 mL of D.I. water. The resulting mixture was stirred at room temperature for 3 hours.

Into a 1L 3-neck round bottom flask equipped with a water cooled/low temperature condenser sequence (dry ice/ isopropanol bath), mechanical

stirrer and rubber septum were placed 18.3 g of $Ca(NO_3)_2 \cdot 4H_20$ and 0.7 g of $Mn(NO_3)_2 \cdot XH_2O$ in 468 mL of D.I. water (Ca/Mn mole ratio=19/1, Ca + Mn = 0.081 moles). The resulting solution was heated to reflux. The phosphate/hydroxide mixture was then added dropwise over approximately one hour with a peristaltic addition pump. The reaction mixture was cooled to room temperature and stirred overnight. The solution was then treated with 0.54 M HEDP (pH 6.6, 1-1.2 Ca/HEDP mole ratio) and stirred at room temperature for one hour.

The reaction mixture was then divided among six 50mL plastic centrifuge tubes and centrifuged for 15 minutes at 2400 rpm. The procedure was repeated with the remainder of the reaction mixture. The almost clear supernatant was discarded and the solid in each tube resuspended to 50 mL of volume with D.I. water and re-centrifuged. The milky wash was set aside and the solid washed twice more. The three washes were combined and then centrifuged at 7000 rpm for 30 minutes. The particles remained pelleted and the clear supernatant was decanted. The solid was resuspended in water and re-centrifuged three more times at 7000 rpm discarding the supernatant after each washing. After the centrifuge workup the solid particles were resuspended in 20-30 mL of D.I. water and then subjected to routine analysis.

Characterization of the particle suspension gave the following results:

size (average diameter, nm): 258

relaxivity ($mMolar^{-1}$ sec^{-1}): 3.05

[Mn] (mole/liter): 0.11

[Ca] (mole/liter): 3.29

% Mn (mole % relative to Ca): 3.35

In magnetic resonance imaging studies, a 45% enhancement of the liver was observed 4 hours post injection at a dose of 10 μmoles Mn/Kg animal body weight.

Example 14

Preparation at room temperature of Hydroxyapatite particles Doped with Mn and treated with HEDP

Manganese containing hydroxyapatite particles were prepared by the following general procedure. A procedure is described for particles containing 10% Mn but other percentages are also applicable.

Into a 1L erlenmeyer flask were placed 10.5 g of $(NH_4)_2HPO_4$, 100 mL of concentrated NH_4OH and 350 mL of D.I. water. The mixture was stirred for two hours with a continuous heavy argon flow (degassing). In a separate 1L erlenmeyer flask were placed 28.9 g of $Ca(NO_3)_2 \cdot 4H_2O$ and 2.4 g of $Mn(NO_3)_2 \cdot XH_2O$ in 400 mL of D.I. water. The metal nitrate solution was degassed with argon for 2 hours. The phosphate solution was then added dropwise to the rapidly stirred metal nitrate mixture over two hours with a peristaltic pump. A continuous argon flow was maintained throughout the course of the reaction. The reaction mixture was stirred for an additional two hours after the addition was complete.

A solution of 8.3 g of a 60% solution HEDP (acid form) in 25 mL of D.I. water was degassed for 30 minutes then added in one aliquot to the hydroxyapatite mixture. The resulting slurry was stirred for 15 minutes. The entire reaction mixture was centrifuged at one time at 2400 rpm for 15 minutes. The supernatant was discarded and the solid residue in each tube resuspended in water. The slurry was re-centrifuged at 2400 rpm and the milky supernatant was collected. The solid was resuspended twice more and centrifuged at 2400 rpm. The three washes were combined and centrifuged at 7000 rpm for 30 minutes. The solid pellet was washed/centrifuged three times and the supernatants discarded. After washing, the solid pellet was suspended in 30 mL of D.I. H_2O.

Characterization of the particulate suspension produced the following

results:

size (average diameter, nm): 229

relaxivity (mMolar-1 sec-1): 29.4

[Mn] (mole/liter): 0.027

[Ca] (mole/liter): 0.377

% Mn (mole % relative to Ca): 6.71

In magnetic resonance imaging studies, a 45% enhancement of the liver was observed immediately post injection at a dose of 10 μmoles Mn/Kg animal body weight.

Example 15

Preparation at room temperature of Hydroxyapatite Doped with 10% Mn(II), Modified by Surface-Adsorbed Mn(II) and HEDP Addition

An ammonium phosphate solution was prepared by dissolving 5.3 grams $(NH_4)_2HPO_4$ in 175 mL of D.I. water. To this was added 50 mL of concentrated NH_4OH with stirring. This solution was degassed for 2 hours (argon bubbling) with stirring and then added dropwise (over 2 hours) via a peristaltic pump (Masterflex) to a solution of 1.27 grams $Mn(NO_3)_2 \cdot H_2O$ and 14.5 grams $Ca(NO_3)_2 \cdot 4H_2O$ in 200 mL of H_2O that had also been deaerated for 2 hours with argon as it was stirred rapidly with a mechanical stirrer. Argon bubbling was continued during the addition. The reaction mixture was stirred for an additional 2 hours as the Ar bubbling continued. 1.27 g $Mn(NO_3)_2 \cdot H_2O$ in 25 mL of deaerated H_2O was added in one portion to the reaction slurry, followed, after 15 minutes, by 4.3 grams of a 60% HEDP solution in water dissolved in 10 mL of deaerated H_2O. The reaction mixture was centrifuged at 2300 rpm and the nearly-clear supernatant discarded. The resulting white, pelleted solid was slurried with water and completely broken up by means of a vortex mixer. The mixture was again centrifuged and the cloudy

supernatant collected. The washing was repeated two separate times. All three washings were saved as was the remaining solid in the centrifuge tubes.

In magnetic resonance imaging studies, a 30% enhancement of the liver was observed immediately post injection at a dose of 10 μmoles Mn/Kg animal body weight.

Example 16

Preparation at 100°C of Hydroxyapatite Particles Modified by Surface-Adsorbed Mn(II) and HEDP Addition

Into a 250 mL erlenmeyer flask were placed 6.3 g of $(NH_4)_2HPO_4$ in 120 mL of D.I. water. Concentrated NH_4OH (60 mL) was added to the mixture followed by 90 mL of D.I. water. The solution was stirred at room temperature for four hours.

Into a 1L 3-neck round bottom flask equipped with a water-cooled and low temperature condenser sequence (dry ice/isopropanol), mechanical stirrer, and rubber septum were placed 19.0 g of $Ca(NO_3)_2 \cdot 4H_2O$ in 468 mL of D.I. H_2O. The mixture was heated to reflux and the phosphate/ammonium hydroxide solution added dropwise with a peristaltic pump and rapid stirring over one hour. The heating was removed when the addition was complete. The reaction mixture was cooled to room temperature then stirred overnight.

The pH of the hydroxyapatite slurry was adjusted from 9.50 to 8.70 with 80 mL of 0.5 N HCl. 2.1 g of $Mn(NO_3)_2 \cdot XH_2O$ in 5 mL of H_2O was added to the hydroxyapatite mixture and stirred for four hours. The reaction mixture became light brown in color. A solution of HEDP (0.54 M, Ca/HEDP mole ratio=1.1) was added and the resulting reaction mixture stirred at room temperature for 3 hours. The color of the slurry became purple/brown.

The reaction mixture was divided among six 50 mL plastic centrifuge tubes and centrifuged for 15 minutes at 2400 rpm. The supernatant was deep

purple and clear. The solid residue was washed/centrifuged three times with 50 mL volumes of water per tube and the three washes combined. The combined washes were centrifuged at 7000 rpm for 20 minutes. The solid pellets were washed/centrifuged three additional times discarding the supernatant after each centrifuge run. The white solid residue was suspended in 15 mL of D.I. H_2O then subjected to routine analyses.

The analyses of the manganese adsorbed hydroxylapatite slurry gave the following results:

size (average diameter, nm): 259
relaxivity ($mMolar^{-1}$ sec^{-1}): 13.8
[Mn] (mole/liter): 0.010
[Ca] (mole/liter): 1.60
% Mn (mole % relative to Ca): 0.66

Example 17

Preparation at Room Temperature of Hydroxyapatite Doped with 10% Mn(II), Modified by Sequential Addition of Mn(II) and HEDP With Washings Between Steps

The general procedure is the same as in Example 15. Before addition of the additional $Mn(NO_3)_2$, however, the reaction mixture was pH adjusted from 9.8 to a lower pH (7.5-9.5) and the mixture then centrifuged, the resulting solid washed with D.I. water, the $Mn(NO_3)_2$ added with stirring under argon bubbling, the resultant mixture centrifuged and the solid washed with water. In the final step the HEDP was added to the slurried solid and then the excess washed away with the supernatant during centrifugation.

In the preparation where the pH was adjusted to 9.5, 5.3 grams $(NH_4)_2HPO_4$ was dissolved in 175 mL of D.I. water. To this was added 50 mL

of concentrated NH_4OH with stirring. This solution was degassed for 2 hours (argon bubbling) with stirring and then added dropwise (over 2 hours) via a peristaltic pump (Masterflex) to a solution of 1.27 grams $Mn(NO_3)_2 \cdot H_2O$ and 14.5 grams $Ca(NO_3)_2 \cdot 4H_2O$ in 200 mL of H_2O that had also been deaerated for 2 hours with argon as it was stirred rapidly with a mechanical stirrer. Argon bubbling was continued during the addition. The reaction mixture was stirred for an additional 2 hours as the argon bubbling continued. The pH of the reaction mixture was adjusted from 9.8 to 9.0 with 3.N HCl with rapid stirring and argon bubbling.

1.27 g $Mn(NO_3)_2 \cdot H_2O$ in 25 mL of deaerated H_2O was added in one portion to the reaction slurry, followed, after 60 minutes, by centrifugation and one washing of the resultant solid (via vortex mixing and recentrifugation). The solid was suspended in water and treated with 4.3 grams of a 60% HEDP solution in water dissolved in 10 mL of deaerated H_2O. After 15 minutes the reaction mixture was centrifuged at 2300 rpm and the nearly-clear supernatant discarded. The resulting white, pelleted solid was slurried with water and completely broken up by means of a vortex mixer. The mixture was again centrifuged and the cloudy supernatant collected. The washing was repeated two separate times. All three washings were combined and the solids from those washings pelleted by centrifugation at 7000 rpm. The resulting pellet was washed with water 3 times by suspension followed by centrifugation at 7000 rpm. The particles were analyzed and found to have an average particle size of 251 nm and a relaxivity, $R_1 = 25\ mM^{-1}sec^{-1}$.

Example 18

Preparation at 100°C of Hydroxyapatite Particles Modified by Surface-Adsorbed Mn, Purified, then Treated with HEDP

Calcium hydroxyapatite particles were prepared by the following procedure:

A solution containing 6.5 g of $(NH_4)_2HPO_4$ in 120 mL of D.I. water was treated with 60 mL of concentrated NH_4OH followed by 90 mL of D.I. water. The resulting solution was stirred for 3 hours at room temperature.

Into a 3-neck 1L round bottom flask equipped with a water cooled and low temperature condenser sequence (dry ice/isopropanol), mechanical stirrer and rubber septum were placed 19.4 g of $Ca(NO_3)_2 \cdot 4H_2O$ in 468 mL of D.I. water. The solution was heated to reflux. The phosphate mixture was added to the rapidly stirred calcium nitrate solution dropwise with a peristaltic pump over one hour. The heat was removed when the addition was complete and the reaction mixture cooled to room temperature. The hydroxylapatite slurry was stirred overnight at room temperature.

The pH of the reaction mixture was decreased from 9.53 to 8.50 with 169 ml of 1N HCl. Manganese nitrate, $Mn(NO_3)_2 \cdot xH_2O$ (2.10 g) was added to the hydroxyapatite mixture and stirred for 1 hour and 15 minutes. The color of the slurry became pale tan. The mixture was then centrifuged at 2400 rpm for 15 minutes. The clear colorless supernatant was discarded and the solid washed/centrifuged with 3-50 mL aliquots of water at 2400 rpm for 15 minutes per run. Half of the solid residue was suspended in 200 mL of D.I. water and stirred vigorously then placed in an ultrasonic bath for 10 minutes to break apart any large clumps. The solid slurry was then treated with 0.54 M HEDP (Ca/HEDP mole ratio=1.2) and stirred for 1.5 hours. The color of the mixture became pale pink/purple. The remaining half of the solid hydroxyapatite pellet was suspended in 200 mL of D.I. H_2O and set aside for

characterization and analyses.

The HEDP treated hydroxyapatite fraction was divided among six 50 mL plastic centrifuge tubes and centrifuged for 15 minutes at 2400 rpm. The supernatant was deep purple and slightly cloudy. The solid residue was suspended in H_2O and centrifuged at 7000 rpm for 30 minutes. The supernatant was discarded and the solid pellet washed/centrifuged three more times at 7000 rpm. The purified hydroxyapatite was suspended in approximately 30 mL of D.I. water then characterized. The results of the analyses are listed below.

	HEDP treated		untreated
size (average diameter, nm):	216		34,100
relaxivity ($mMolar^{-1}$ sec^{-1}):	38.3		0.78
[Mn] (mole/liter):	0.0025		0.016
[Ca] (mole/liter):	0.170	0.638	
% Mn (mole % relative to Ca):	1.44		2.45

In magnetic resonance imaging studies, a 25% enhancement of the liver was observed immediately post injection at a dose of 10 μmoles Mn/Kg animal body weight.

Example 19

Preparation of Mn-Doped Hydroxyapatite Particles Having a Functionalized Coating Agent

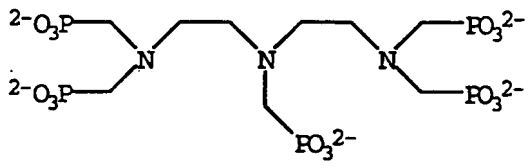
This example describes the general preparation of hydroxyapatite particles having a functionalized coating agent. The particles are prepared by adding 0.1-100 mole % of an appropriate coating agent to a slurry of Mn(II) substituted hydroxyapatite with 0.1-100 mole % Mn based on the Ca used in

the reaction. The mixture is stirred from 1 to 360 minutes at temperatures in the range from 4°C to 100°C and the solid separated from the supernatant by centrifugation. The resulting solid is collected or subjected to repeated washings with water to remove excess ions and coating agent. The solid, after resuspension in water, may be treated with a metal salt (0.01-10 mole% based on Ca in the preparation). This is especially appropriate if the coating agent contains a pendant chelating group to capture and hold tightly the metal (when subjected to in vitro and/or in vivo solutions). The resultant solid is separated by centrifugation and washed 3 times with water to remove loosely attached coating agent or free metal/coating agent complex.

Example 20

Preparation of Hydroxyapatite Particles treated with Diethylenetriamine-penta(methylenephosphonic acid) Followed by Surface Adsorption of Mn

Calcium hydroxyapatite was prepared by the following procedure then treated with the functionalized polyphosphonate, diethylenetriamine-penta(methylene-phosphonic acid), abbreviated DETAPMDP and having the following structure:



A basic ammonium phosphate solution was prepared using 6.34 g of $(NH_4)_2HPO_4$ in 120 mL of D.I. water. Concentrated ammonium hydroxide (60 mL) was added followed by 90 ml of D.I. water. The mixture was stirred for 4 hours at room temperature.

A solution of 19.0 g of $Ca(NO_3)_2 \cdot 4H_2O$ in 468 mL of D.I. water was placed in a 3-neck 1L round bottom flask. The reaction setup included a mechanical stirrer, water cooled and low temperature (dry ice/isopropanol) condenser arrangement, and a rubber septum. The solution was heated to reflux with rapid stirring. The basic phosphate solution was added dropwise with a peristaltic pump over one hour. The heat was removed after the addition was complete and the reaction mixture stirred overnight at room temperature.

The hydroxyapatite slurry was treated with a solution of DETAPMDP (Ca/DETAPMDP mole ratio=1.1, pH of DETAPMDP 6.3) and stirred at room temperature for 2.5 hours. The phosphonate treated mixture was then reacted with $Mn(NO_3)_2 \cdot XH_2O$ (Ca/Mn mole ratio=2.3) and stirred for an additional 3.5 hours.

The reaction mixture was divided among six 50 mL plastic centrifuge tubes and centrifuged at 2400 rpm for 15 minutes. The clear supernatant was discarded and the solid residue suspended in 50 mL of D.I. per tube and centrifuged at 2400 rpm. The milky suspension was decanted and set aside. The solid was washed/centrifuged twice more and the three washes combined. The milky suspension was re-centrifuged at 7000 rpm for 30 minutes. The clear supernatant was discarded and the solid pellet resuspended and centrifuged three additional times at 7000 rpm. The purified pellet was then suspended in 15 mL od D.I. water and analyzed. The following results were obtained.

clear supernatant was discarded and the solid pellet resuspended and centrifuged three additional times at 7000 rpm. The purified pellet was then suspended in 15 mL od D.I. water and analyzed. The following results were obtained.

size (average diameter, nm): 258

relaxivity ($mMolar^{-1}$ sec^{-1}): 20.3

[Mn] (mole/liter): 0.0013

[Ca] (mole/liter): 1.921

% Mn (mole % relative to Ca): 0.07

In magnetic resonance imaging studies, a 30% enhancement of the liver was observed immediately post injection at a dose of 10 μmoles Mn/Kg animal body weight.

Example 21

Replacement of Phosphate with Arsenate in Preparation of Hydroxyapatite and Substituted Hydroxyapatites

The procedure according to Example 14 is used except that 0.1-100 mole % arsenate is substituted for the phosphate. For example, 9.51 grams $(NH_4)_2HPO_4$ and 1.49 grams Na_2AsO_4 were dissolved in 400 mL of D.I. water. To this was added 100 mL of concentrated NH_4OH with stirring. The rest of the procedure follows directly from Example 14.

Example 22

Replacement of Phosphate with Vanadate in Preparation of Hydroxyapatite and Substituted Hydroxyapatites

The procedure according to Example 14 is used except that 0.1-100 mole percent vanadate is substituted for the phosphate. For example, 9.51 grams $(NH_4)_2HPO_4$ and 1.40 grams Na_3VO_4 were dissolved in 400 mL of D.I. water. To this was added 100 mL of concentrated NH_4OH with stirring. The rest of

the procedure follows directly from Example 14.

Example 23

Preparation at 100°C of Mn-Doped Fluoroapatite Particles

Manganese fluoroapatite was prepared by the following general procedure. Into a 5-neck 1L round bottom flask equipped with a mechanical stirrer, water cooled reflux condenser, adapter for pH electrode, and two rubber septa for addition of reagents were placed 10.3 g of $Mn(OAC)_2 \cdot 4H_20$ in 200 mL of D.I. water. The solution was degassed with heavy argon bubbling for 30 minutes. A solution of ammonium fluoride, NH_4F (0.3 g) in 50 mL of D.I. water was prepared in a 125 mL erlenmeyer flask and degassed for 30 minutes with argon. Into a 250 mL erlenmeyer flask was placed 3.3 g of $(NH_4)_2HPO_4$ in 150 mL of D.I. water and degassed for 30 minutes before addition.

The manganese acetate solution was heated to reflux with rapid stirring (pH 6.6) and the NH_4F and $(NH_4)_2HPO_4$ solutions were added dropwise simultaneously with a peristaltic pump over 35 minutes. The solid precipitated among immediate addition of reagents and was pale pink in color. The pH of the reaction mixture dropped to 4.7 by the end of the reaction. The heating was stopped when the addition was complete. The reaction mixture was stirred at room temperature overnight.

The apatite slurry was divided among four 50 mL plastic centrifuge tubes and centrifuged for 30 minutes at 2400 rpm. The clear supernatant was discarded, and the pale pink solid was resuspended and centrifuged for 30 minutes at 2400 rpm. The solid was washed and centrifuged twice more and the clear supernatants discarded. The purified solid pellet was suspended in 20 mL of D.I. water.

Example 24

Preparation of Radiolabeled Mn-Hydroxyapatite Particles

Using the pre-formed method described above, a stabilizer (gentisic acid), a reductant (stannous) and a transfer agent (citrate) and the appropriate ligand were placed in a vial under an inert atmosphere. 188-Re or 186-Re as perrhenate was injected into the vial. This solution was heated for 15 to 30 minutes in a boiling water bath. The contents of the vial were removed with a syringe and injected into a second vial which contains the Mn-hydroxyapatite particles prepared in Example 4 in an appropriate buffer solution. The contents of the second vial were heated so as to effect covalent bonding of the metal chelate complex to the particle. Quality controls (tlc) were performed on the contents of this second vial. The radiolabeled Mn-hydroxyapatite particles were suspended in a solution that is physically acceptable for injection.

Example 25

Preparation of Radiolabeled Mn-Hydroxyapatite Particles

Using the post-formed method described above, properly sized Mn-hydroxyapatite particles as described in Example 4 were slurried in a buffer solution with an excess of ligand that was activated in a fashion such that conjugation of the ligand to the particle was effected. This solution containing the resulting particle-ligand moiety was injected into a vial which contained a stabilizer, a transfer ligand and a reductant and into which perrhenate had been added in a previous step. The contents of this second vial ware heated so as to effect covalent attachment of the radiorhenium to the particle-bonded chelate. The radiolabeled Mn-hydroxyapatite particles were suspended in a solution that is physically acceptable for injection.

Example 26

Preparation of Radiolabeled Mn-Hydroxyapatite Particles

Using the pre-formed method, described above, a radiorhenium-HEDP complex was prepared by adding an aliquot of radiorhenium to a solution that contains ≤ 10 mg HEDP, ≤3 mg of $SnCl_2$, and ≤ 10 mg of gentisic acid. This solution was heated in either an autoclave at 120°C, or a boiling water bath (or heating block) at 100°C for 15 min. to 1 hour, or in a microwave oven for 2 minutes. An aliquot of this solution was added to a slurry that contains from 10 to 100 mg of Mn-hydroxyapatite particles as described in Example 4 which have been suspended in water to which a 1% dispersant such as Triton-X, Tween-80 has been added. The slurry was stirred at room temperature for up to 30 minutes before the particles were collected and washed by centrifugation and/or filtration. The particles were resuspended in an injectable matrix prior to use as a synovectomy agent.

Example 27

Preparation of Radiolabeled Mn-Hydroxyapatite Particles

Using the pre-formed method described above, 200 µl of $^{153}SmCl_3$ was added to 600 µl Citrate solution (25 mg/ml) and the solution vortexed and incubated for 30 minutes at room temperature. The pH of the solution was then raised to approximately 4 or 5. Forty (40) mg of Mn-hydroxyapatite (10-20 µ) as described in Example 4, 750 µl H_2O and 250 µl ^{153}Sm-citrate transfer ligand complex were combined in 15 ml polystyrene centrifuge tubes containing stir bars and the slurry was stirred at room temperature for up to 30 minutes before the particles were collected and washed by centrifugation and/or filtration. The particles were resuspended in an injectable matrix prior to use as a synovectomy agent.

Example 28

Preparation of Radiolabeled Mn-Hydroxyapatite Particles

Using the post-formed method described above, a specific example of this preparation involves the following process: Mn-hydroxyapatite particles as described in Example 4 were slurried with 600 µl Citrate solution (25 mg/ml) for up to 30 minutes. The particles were removed by centrifugation or filtration and washed to remove the excess ligand. The ligand bonded particles were then added to a solution containing 200 µl of $^{153}SmCl_3$. After the formation of the ligand bonded particle-radioisotope composition the particles are collected and washed by centrifugation and/or filtration. The particles were resuspended in an injectable matrix prior to use as a synovectomy agent.

The invention may be embodied in other specific forms without departing from its spirit or essential characteristics. The described embodiments are to be considered in all respects only as illustrative and not restrictive. The scope of the invention is, therefore, indicated by the appended claims rather than by the foregoing description. All changes which come within the meaning and range of equivalency of the claims are to be embraced within their scope.

What is claimed is:

1. A composition comprising an apatite particle having the following general formula:

$$Z\text{-}Ca_nM_mX_rY_s$$

wherein M is a paramagnetic ion or stoichiometric mixture of metal ions having a valence of 2+ or 3+, X is a simple anion, Y is a tetrahedral oxyanion, carbonate, tetrahedral anion, or mixtures thereof, m is from 1-10, n is from 1-10, where M is a 2+ metal ion, then m + n = 10, and where M is a 3+ metal ion, then m + 1.5n = 10, r and s are adjusted as needed to provide charge neutrality, and Z is a β-emitting radionuclide.

2. A composition as defined in claim 1, wherein M is selected from a group of elements having atomic numbers of 21-25, 27-29, 42-44, and 58-70 and a valence in the range from 2+ to 3+.

3. A composition as defined in claim 1, wherein M is chromium(III), manganese(II), iron(II), iron(III), praseodymium(III), neodymium(III), samarium(III), ytterbium(III), gadolinium(III), terbium(III), dysprosium(III), holmium(III), or erbium(III).

4. A composition as defined in claim 1, wherein M is manganese(II), iron(II), iron(III), or mixtures thereof.

5. A composition as defined in claim 1, wherein X is selected from the group consisting of OH^-, F^-, Br^-, I^-, $\frac{1}{2}[CO_3^{2-}]$, or mixtures thereof.

6. A composition as defined in claim 1, wherein Z is selected from the group consisting of 198-Au, 188-Re, 186-Re, 177-Lu, 176m-Lu, 175-Yb, 169-Er, 166-Ho, 165-Dy, 156-Sm, 153-Sm, 115m-In, 105-Rh, 90-Y, 51-Cr, 77-As, 67-Cu, 32-P, 141-Ce, 144-Pr, 147-Nd, 148-Pm, 152-Eu, 153-Gd, 157-Tb and 170-Tm.

7. A composition as defined in claim 1 wherein Z is covalently bound to the apatite particle by a chelating group.

8. A composition as defined in claim 7 wherein the chelating group is selected from the group consisting of phosphonate carboxylate and amine carboxylate ligands, citrate, MAG_3 (mercaptoacetylglycylglycylglycine), polycarboxylic acid-amine ligands, mono- and poly-phosphonates, BATs (N,N'-bis(2-mercapto-ethyl)ethylene-diamine), thiosemicarbazones, amine-oxime ligands, marcocyclic and open chain tetra-, penta-, hexa-, hepta- and octacoordinating nitrogen-containing compounds with or without other coordinating atoms or unsaturation.

9. A composition as defined in claim 8 wherein the chelating group is citrate.

10. A composition as defined in claim 9 wherein Z is Sm-153.

11. A composition as defined in claim 1 wherein the apatite particles have a particle size of about 0.5 to about 40 microns.

12. A method for simultaneous magnetic resonance imaging and radiation synovectomy of an inflamed synovium comprising:

(a) administering to a patient, a diagnostically effective

amount of apatite particles incorporating paramagnetic species and a β-emitting radionuclide therein, in a pharmaceutically acceptable carrier, said apatite particles having a general formula

$$Z\text{-}Ca_nM_mX_rY_s$$

wherein M is a paramagnetic ion or stoichiometric mixture of metal ions having a valence of 2+ or 3+, X is a simple anion, Y is an teterahedral oxyanion, carbonate, tetrahedral anion, or mixtures thereof, m is from 1-10, n is from 1-10, where M is a 2+ metal ion, then m + n = 10, and where M is a 3+ metal ion, then m + 1.5n = 10, r and s are adjusted as needed to provide charge neutrality, and Z is a β-emitting radionuclide; and

(b) imaging the inflamed synovium using magnetic resonance techniques while simultaneously effecting radiation synovectomy of the synovium.

13. The method as defined in claim 12, wherein M is selected from a group of elements having atomic numbers of 21-25, 27-29, 42-44, and 58-70 and a valence in the range from 2+ to 3+.

14. The method as defined in claim 12, wherein M is chromium(III), manganese(II), iron(II), iron(III), praseodymium(III), neodymium(III), samarium(III), ytterbium(III), gadolinium(III), terbium(III), dysprosium(III), holmium(III), or erbium(III).

15. The method as defined in claim 12, wherein M is manganese(II), iron(II), iron(III), or mixtures thereof.

16. The method as defined in claim 12, wherein X is selected from

the group consisting of OH^-, F^-, Br^-, I^-, $\frac{1}{2}[CO_3^{2-}]$, or mixtures thereof.

17. The method as defined in claim 12, wherein Z is selected from the group consisting of 198-Au, 188-Re, 186-Re, 177-Lu, 176m-Lu, 175-Yb, 169-Er, 166-Ho, 165-Dy, 156-Sm, 153-Sm, 115m-In, 105-Rh, 90-Y, 51-Cr, 77-As, 67-Cu, 32-P, 141-Ce, 144-Pr, 147-Nd, 148-Pm, 152-Eu, 153-Gd, 157-Tb and 170-Tm.

18. The method as defined in claim 12 wherein Z is covalently bound to the apatite particle by a chelating group.

19. The method as defined in claim 18 wherein the chelating group is selected from the group consisting of phosphonate carboxylate and amine carboxylate ligands, citrate, MAG_3 (mercaptoacetylglycylglycylglycine), polycarboxylic acid-amine ligands, mono- and poly-phosphonates, BATs (N,N'-bis(2-mercapto-ethyl)ethylene-diamine), thiosemicarbazones, amine-oxime ligands, marcocyclic and open chain tetra-, penta-, hexa-, hepta- and octacoordinating nitrogen-containing compounds with or without other coordinating atoms or unsaturation.

20. The method as defined in claim 19 wherein the chelating group is citrate.

21. The method as defined in claim 20 wherein Z is Sm-153.

22. The method as defined in claim 12 wherein the apatite particles have a particle size of about 0.5 to about 40 microns.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/10808

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61B 5/055; A61K 51/00
US CL :424/9.364, 9.32, 1.29, 9.3
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/9.364, 9.32, 1.29, 9.3, 9.322, 9.323, 1.37; 128/653.4, 654; 423/263

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, CAPLUS, MEDLINE, BIOSIS
search terms: apatite, radiotherapy, radionuclide, radiation, therapy, MRI, NMR, magnetic resonance, synovectomy

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,320,824 A (BRODACK ET AL.) 14 June 1994 (14.06.94), see abstract and column 3, lines 6-50.	1-22
Y	US 5,342,609 A (MEEH ET AL.) 30 August 1994 (30.08.94), see abstract and columns 3-4.	1-22
Y, P	US 5,520,904 A (NOSCO ET AL.) 28 May 1996 (28.06.96), see entire document.	1-22

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
04 SEPTEMBER 1996	25 SEP 1996
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer Michael G. Hartley Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*